REMARKS

Applicants have carefully studied the Office Action mailed on September 17, 2008 which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Amendments to the Specification

Paragraph [0053] of the specification has been amended to recite the correct sequence corresponding to SEQ ID NO: 2. Such correct sequence is present in the corresponding paragraph of the PCT Application No. PCT/US2004/019934 (see top paragraph at p. 16 of WO 2004/112728). Such correct sequence is also recited in various other parts of the specification (see, e.g., paragraphs [0055], [0064], and [0162]). No new matter has been added as a result of this amendment.

Pending Claims

Claims 1-17 were pending and at issue in this application. Claims 1-4 and 8-17 have been withdrawn from consideration as drawn to a non-elected invention. Claim 5 has been rejected for lack of enablement. Claims 5-7 have been rejected as being anticipated and/or obvious over prior art.

To expedite prosecution, claim 5 has been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of this claim in a continuing application.

Claims 6 and 7 have been amended by adding the amino acid sequences corresponding to the recited SEQ ID NOS and to correct typographical errors. Claim 6 has also been amended to specify that the encompassed peptides are "derived from the ankyrin binding domain of an L1-CAM family member protein" and "promote neurite outgrowth". Support for these limitations can be found, for example, in paragraphs [0053-0055], [0057], Example 8 (paragraphs [0166-0172],

especially paragraph [0172]), and Figure 6 of the application (see the application as published, US 2006-0142189). Claim 7 has been further amended to depend from claim 6.

Withdrawn claims 1-4 and 8-17 have been amended to correct various typographical errors. Claims 1-3, 8-10 and 16-17 have been also amended to refer to the peptide of claim 6 and thus clarify the connection between the method and composition claims. Claims 13-15 have been amended to correct dependency.

New claims 18-25 have been added. New claim 19 recites "an isolated peptide consisting essentially of an amino acid sequence QFNEDGSFIGQF (SEQ ID NO: 2), wherein said peptide promotes neurite outgrowth." New claim 20 depends from claim 19 and further limits the sequence of the peptide. New claims 22-24 depend from claim 6 and further limit the sequence of the peptide. Support for claims 19, 20 and 22-24 can be found, for example, in paragraphs [0053-0055], [0057], Example 8 (paragraphs [0166-0172], especially paragraph [0172]), and Figure 6 of the application.

New claims 18 and 21 recite pharmaceutical compositions comprising the peptides of claim 6 or 19, respectively, and a pharmaceutically acceptable carrier. Support for these claims can be found, for example, in the original claim 5 and paragraphs [0015], [0058], and [0087-0088] of the specification.

New claim 25 depends from claim 3 and further limits the diseases characterized by axonal damage to those selected from the group consisting of spinal cord injury, traumatic brain injury, stroke, and neurodegenerative diseases. Support for this new claim can be found, for example, in the original claim 3 as well as in paragraphs [0009] and [0058] of the specification.

No new matter has been added as a result of these amendments. As a result of these amendments, claims 1-4 and 6-25 will be pending.

Restriction Requirement

In the present Office Action, despite applicants' traversal, the Examiner has maintained the restriction between the provisionally elected product claims 5-7 and process claims 1-4 and 9-18 arguing that process claim 1 cannot share a special technical feature with the other claimed inventions, because it does not recite a special technical feature over the prior art. Specifically, the Examiner contends that US Patent No. 6,576,607 discloses the method of promoting neurite outgrowth using L1-CAM and that the claimed peptide comprising SEQ ID NO: 2 is known from the prior art disclosure of the full-length L1-CAM family member having the Y->F mutation in the FIGQY motif in Tuvia et al. (Proc. Natl. Acad. Sci. USA, 1997, 94:12957-12962) and Garver et al. (J. Cell Biol., 137:703-714).

In response, applicants respectfully note that the only argument presented by the Examiner relates to claim 1. It is not clear from the Office Action why the restriction is maintained with respect to process claims 2-4 and 9-18 and product claim 8 none of which depend from claim 1. Clarification is respectfully requested.

With respect to the alleged lack of novelty of claim 1, applicants respectfully disagree with the Examiner. This claim as amended recites "a method for promoting outgrowth of a mammalian neuron comprising contacting said neuron with the peptide of claim 6." Claim 6 has been, in turn, amended to recite "an isolated peptide derived from the ankyrin binding domain of an L1-CAM family member protein comprising an amino acid sequence QFNEDGSFIGQF (SEQ ID NO: 2), wherein said peptide promotes neurite outgrowth." As clarified by these amendments, the present claims do not encompass the full-length L1-CAM or any other full-length L1-CAM family member proteins comprising the Y->F mutated FIGQY motif, but relate only to peptides derived from the ankyrin binding domain of an L1-CAM family member protein which promote neurite outgrowth. The prior art references cited by the Examiner do not disclose or suggest such peptides or their use for promoting outgrowth of mammalian neurons. Accordingly, these claims are novel over the cited prior art (see a more detailed discussion in connection with the anticipation and obviousness rejections, below).

Applicants therefore respectfully request reconsideration of the Restriction Requirement to allow examination of all groups of claims in the same application.

According to USPTO examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803).

By the present amendment all method claims (claims 2-4 and 9-18) and the nucleic acid claim 8 have been amended to refer to the peptide of claim 6. Thus, the search for any of these claims would necessarily be co-extensive with the search for claim 6 and examination of these groups together would not be an undue burden on the Examiner. Accordingly, applicants respectfully request that the Examiner withdraws the Restriction Requirement to allow prosecution of all pending claims together in the same application.

Applicants also respectfully acknowledge the Examiner's statement that where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104.

Objection to the Drawings

In the Office Action, the Examiner has objected to the drawings based on 37 C.F.R. §§ 1.58(a) and 1.83 stating that sequence listings included in the specification should not be duplicated in drawings 7A, 7B, 8A and 8B.

In response, applicants respectfully note that the present application is a U.S. National Phase application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2004/019934, filed June 21, 2004. As specified in 37 C.F.R. § 1.83(a), "tables and sequence listings that are included in the specification are, except for applications filed under 35 U.S.C. 371, not permitted to be included in the drawings" (emphasis added).

Withdrawal of the objection is therefore respectfully requested based on the § 371 exclusion.

Objection to the Abstract

The Examiner has objected to the abstract, because the abstract contains more than 150 words. In response, the abstract has been amended decreasing the number of words to below 150.

Objection to the Title

The Examiner has also objected to the title arguing that the elected invention is directed to an isolated peptide, which is a product not a process. In response, the title has been amended to recite "PEPTIDES FOR TREATING AXONAL DAMAGE, INHIBITION OF NEUROTRANSMITTER RELEASE AND PAIN TRANSMISSION, AND BLOCKING CALCIUM INFLUX IN NEURONS" (emphasis added).

Claim Objections

Claim 5 has been objected to, because the article "an" is missing before the limitation "peptide" as recited in the line 3 of the claim.

Since claim 5 has been canceled, the objection to this claim is rendered moot.

Enablement Rejection

In the Office Action, the Examiner has rejected claim 5 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the present application, while being enabling for a pharmaceutical composition comprising an isolated peptide comprising or consisting of SEQ ID NO:2 to promote neurite outgrowth in neurons in vitro or in vivo, does not reasonably provide enablement for a pharmaceutical composition comprising SEQ ID NO:2 for treating all forms of diseases characterized by axonal damage selected from spinal cord injury, traumatic brain injury, stroke and neurodegenerative diseases. The Examiner argues that the application fails to establish that all different diseases caused by different mechanisms can be treated with the same drugs, because the level of predictability in the art is very low.

Without admitting the correctness of the Examiner's rejection and simply to expedite the prosecution, claim 5 has been canceled without prejudice or disclaimer. Accordingly, the rejection of this claim is rendered moot.

Applicants reserve the right to pursue the subject matter of canceled claim 5 in a continuing application.

For the record, applicants note that the present application fully enables the use of the peptides of the present invention to treat spinal cord injury, traumatic brain injury, stroke, and neurodegenerative diseases, because, regardless of the clinical manifestations, all of these diseases are characterized by axonal damage and the peptides of the invention can treat these diseases by promoting outgrowth of the damaged axons and re-establishment of the damaged neuronal connections. Indeed, as stated in paragraph [0058] of the specification,

> The ability to directly modulate L1-CAM-ankyrin binding using the peptide compounds of the invention has important implications in the treatment of various disease states characterized by axonal damage such as spinal cord injury, traumatic brain injury, stroke, and neurodegenerative disease. In these conditions, the axons of a neural cell may be severed or degraded. The neuron is alive but will be degraded from the site of injury back to the undamaged cell body. The use of the peptides of the invention enables neuronal outgrowth of the damaged axon out towards its proper connection. Thus, the present invention also provides a method for the treatment of spinal cord injury by administering an amount effective to treat spinal cord injury, traumatic brain injury, stroke, and neurodegenerative disease of the peptides of the invention to a subject in need of such treatment. By inhibiting the binding of L1-CAM and ankyrin, the peptides promote outgrowth of spinal cord neurons and promote the re-establishment of the damaged neuronal connections.

As specified above, the Examiner has acknowledged that the present specification provides enablement for promoting neurite outgrowth using the claimed peptides (see paragraph bridging pages 5 and 6 of the Office Action). Differences in clinical manifestations between various diseases characterized by axonal damage is therefore irrelevant for the methods of treatment claimed in the present application.

Anticipation Rejections

In the Office Action, claims 5 and 6 have been rejected under 35 U.S.C. § 102(b) as being anticipated by either Tuvia et al. (Proc. Natl. Acad. Sci. USA, 1997, 94:12957-12962) or Garver et al. (J. Cell. Biol., 1997, 137:703-714) as evidenced by Davis et al. (J. Cell. Biol., 1996, 135:1355-1367).

The Examiner alleges that both Tuvia and Garver disclose an L1-CAM family member, neurofascin, comprising a mutation of tyrosine (Y) to phenylalanine (F) in the motif "FIGQY". The Examiner further alleges that, according to Davis, the mutant neurofascin of the Tuvia and Garver references comprises SEQ ID NO: 2. The Examiner concludes that the present claims encompass the full-length L1-CAM family members due to the use of the term "comprising".

As claim 5 has been canceled, the rejection of this claim is rendered moot. With respect to claim 6, the rejection is respectfully traversed for the reasons provided below.

Claim 6 has been amended to clarify that the encompassed peptides are "derived from the ankyrin binding domain of an L1-CAM family member protein" and thus excludes the full-length L1-CAM family member proteins. As stated in paragraph [0053] of the specification (emphasis added),

> The novel peptide of the invention is a peptide *derived from the ankyrin binding domain of the L1 family members* in which the carboxy-terminal tyrosine is substituted with phenylalanine and comprises the amino acid sequence QFNEDGSFIGQF (SEQ ID NO: 2). This amino acid sequence was derived from the 12 amino acid conserved region of the L1-CAM cytoplasmic tail that has been shown to be required for ankyrin binding to other L1-CAM family members (Zhang et al. J Biol Chem 1998;273:30785-30794). The tyrosine to phenylalanine substitution mimics the dephosphorylated, ankyrin-binding protein motif.

Claim 6 as amended further clarifies that the encompassed peptides "promote neurite outgrowth." As disclosed in the present specification, the peptides of the invention when introduced in a cell promote neurite outgrowth by inhibiting the interactions of endogenous full-length L1-CAM family proteins with the cytoskeleton (see, e.g., paragraphs [0015] and [0052] of the

application). Specifically, the FIGQF sequence contained within the peptides of the invention mimics the conserved dephosphorylated FIGQY ankyrin-binding motif of L1-CAM family members and thus functions as a competitive inhibitor of the interaction between the cytoplasmic domains of L1-CAM family proteins and the cytoskeleton linker protein ankyrin. As a result of such inhibition by the peptides of the invention, the endogenous full-length L1-CAM family proteins are able to associate with other proteins in the cytoplasm that are necessary for their activity in the promotion of neurite outgrowth (see, e.g., paragraphs [0049-0050] of the specification).

The clinically relevant neurite growth promoting activity of the peptides of the invention is based on the fact that they disrupt the interactions of the L1-CAM family proteins with the cytoskeleton, but do not disrupt other protein interactions which are needed for functioning of these transmembrane proteins in promoting neurite outgrowth. In contrast, the full-length FIGQY->F mutant neurofascin disclosed in the Tuvia and Garver references not only will block the ankyrin-mediated cytoskeleton binding of the endogenous L1-CAM family proteins, but will also competitively inhibit the interactions needed for promoting neurite outgrowth (e.g., intramembrane and/or extracellular interactions with other transmembrane proteins).

Taken together, claim 6 as amended specifies both structural (i.e., "derived from the ankyrin binding domain of an L1-CAM family member protein") and functional (i.e., "promotes neurite outgrowth") properties of the encompassed peptides. The FIGQY->F mutant neurofascin disclosed in the Tuvia and Garver references is a full-length protein and is therefore excluded from the claimed genus of peptides derived from the ankyrin binding domain of an L1-CAM family protein. Furthermore, in contrast to the peptides recited in the present claims, the FIGQY->F mutant neurofascin disclosed in the Tuvia and Garver references does not promote (and, in fact, inhibits) neurite outgrowth.

Since the Tuvia and Garver references do not disclose or suggest any peptides which fall within the present claims, these references do not anticipate the present claims.

In light of the above arguments and amendments, the anticipation rejections are believed to be overcome and withdrawal of these rejections is respectfully requested.

Obviousness Rejections

In the Office Action, the Examiner has further rejected claims 5-7 under 35 U.S.C. § 103(a) as being unpatentable over Tuvia et al. (Proc. Natl. Acad. Sci. USA, 1997, 94:12957-12962) or Garver et al. (J. Cell. Biol., 1997, 137:703-714) as evidenced by Davis et al. (J. Cell. Biol., 1996, 135:1355-1367) in view of US6025140 (Langel et al.).

Since claim 5 has been canceled, the rejection of this claim is rendered moot.

In the Office Action, the Examiner's analysis is directed only to claim 7. Accordingly, it is believed that there is no separate rejection of claim 6. If this is otherwise, the Examiner is respectfully requested to specify the basis for any remaining obviousness rejections of claim 6.

With respect to claim 7, the Examiner contends that SEQ ID NO: 4 of patent US6025140 is the antennapedia homeodomain pAntp (43-58) which is taught to enhance penetration of peptides containing it into the cell membrane. The Examiner alleges that SEQ ID NO: 4 of patent US6025140 is 100 % identical to SEQ ID NO: 6 of the instant application. The Examiner concludes that it would have been obvious to a skilled artisan to fuse a peptide comprising SEQ ID NO: 2 to a peptide comprising SEQ ID NO: 6 to enhance membrane penetration of the claimed peptide. The Examiner further states that the person of ordinary skill in the art would have been motivated to do so with an expectation of success, because the antennapedia homeodomain comprising SEQ ID NO: 6 has been successfully used to enhance peptide penetration into the cell.

As specified above, claim 7 has been amended to depend from claim 6, and claim 6 has been amended to clarify that the encompassed peptides are "derived from the ankyrin binding domain of an L1-CAM family member protein" and "promote neurite outgrowth". Accordingly, claims 6 and 7 as amended (as well as new claims 22-24 which depend from claim 6) exclude the full-length L1-CAM protein and other full-length L1-CAM family members such as mutant neurofascin disclosed in the Tuvia and Garver references (see the Anticipation Rejections section, above, for a more

detailed explanation). Since none of the references cited by the Examiner disclose or suggest any peptides comprising SEQ ID NO: 2 which fall within the present claims, these references do not make obvious the present claims. The disclosure of the membrane penetration peptide in US6025140 does not supply the missing teaching or motivation with respect to SEQ ID NO: 2.

In light of the above arguments and amendments, the obviousness rejections are believed to be overcome and withdrawal of these rejections is respectfully requested.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that the present claims are in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7634. The Examiner is authorized to charge any additional fees associated with this response or credit any overpayment to our Deposit Account No. 04-0100.

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Respectfully submitted,

By_____

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